Anti-Tumor Activity of Traditional Chinese Medicine, Ekki-Youketsu-Fusei-Zai, and Its Effects on Immunocyte Functions : 1. A Life-Prolonging Effect and Enhancement of NK Cell Function in Tumor-Bearing Mice

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Original

Anti-Tumor Activity of Traditional Chinese Medicine, Ekki-Youketsu-Fusei-Zai, and Its Effects on Immunocyte Functions

1. A Life-Prolonging Effect and Enhancement of NK Cell Function in Tumor-Bearing Mice

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Abstract: We examined anti-tumor effects of the Traditional Chinese Medicine (TCM), Ekki-Youketsu-Fusei-Zai (EYFZ), on survival, tumor size, body weight, and natural killer (NK) cell activity in tumor-bearing mice by using a tumor cell line, colon-26. The significant life-prolonging effect was found, when EYFZ was orally administrated for 28 days, which procedure started just after the subcutaneous implantation of colon-26 cell line. In addition, an oral administration of EYFZ inhibited the tumor growth and the loss of body weight in tumor-bearing mice. The significant increases in splenic NK cell activity of the tumor-bearing mice were also induced by oral administration of EYFZ. These results strongly suggest that EYFZ has the anti-tumor effects on colon-26 implanted mice via augmentation of NK cell activity.

Keywords: Traditional Chinese Medicine (TCM), Ekki-Youketsu-Fusei-Zai (EYFZ), anti-tumor activity, natural killer (NK) cell activity

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Introduction

Some kinds of crude drugs of Traditional Chinese Medicine (TCM) have been so far useful for cancer patients as both an anti-tumor drug and an adjuvant, which greatly enhances the immunological functions of cancer patients[1, 2]. Ekki-Youketsu-Fusei-Zai (EYFZ), one of the TCMs, is a mixture composed of six kinds of crude drugs, which have been used for cancer patients in China. Recent studies have shown that each crude drug has various biological activities. For example, *Astragali radix* has immunologically enhancing and anti-tumor effects[3-5], while *Angelicae radix* has anti-inflammatory, analgesic, interferon inducing, and immunopotentiating effects[6-9]. *Cervi parvum cornu* is known to show anti-tumor and immuno-enhancing effects by inhibiting the monoamine oxidase (MAO) activity[10-12], and *Zizyphi fructus* augments the function of natural killer cell as well as ciliary motility in the airway[13, 14]. Finally, *Rehmanniae radix* is reported to have anti-tumor activity, enhance cytotoxic T lymphocytes (CTL) activity and induce IL-2 production by T cells[15, 16].

Though each component of EYFZ has shown various biological activities and EYFZ has been used for cancer patients, its anti-tumor effects and immuno-enhancing effects have not been investigated. In this study, we examined the effects of oral administration of EYFZ on the survival, tumor size, body weight and natural killer (NK) cell activity of tumor-bearing mice in order to elucidate the relationship between immuno-enhancing effects of EYFZ and its anti-tumor effects.

Materials and Methods

Animals and tumor cell line Specific-pathogen-free BALB/c female mice at the age of 5 weeks, originally purchased from Japan CLEA Co, were used throughout this experiment and approved by institutional animal care committee. Colon-26 cell line, colon-adenocarcinoma from BALB/c mice, was generously provided by Prof.

Kikuo Nomoto, Kyushu University, and cultured *in vitro* with the basal medium (RPMI-1640) containing 10 % fetal bovine serum (FBS), 2.0 g/L $NaHCO_3$, 1.0 g/L HEPES, 0.6 g/L L-glutamine, and 0.25 mg/L Kanamycin. By a strong pipetting procedure, we obtained a single cell suspension and 5×10^5 cells were implanted subcutaneously into the back of mouse. Murine lymphoma YAC-1 cell was maintained in the same culture medium as shown above.

Preparation of EYFZ EYFZ is a mixture composed of six kinds of crude drugs as shown in Table 1. All of the crude drugs were obtained from Tochimoto, Ltd., Osaka, and EYFZ was prepared as follows. First, a mixture of *Astragali radix* (10.0 g), *Zizyphy fructus* (5.0 g), *Amomi semen* (5.0 g), *Angelicae radix* (8.0 g), *Cerve parvum cornu* (5.0 g), and *Rehamnniiae radix* (10.0 g) was added to 200 ml water and soaked for 20 min. Then, it was boiled for 30 min for extraction of effective substances, and filtered. Finally, the extracted solution was condensed to 43 ml (1 g crude drug/ml) by heating evaporation, and orally administered to mice at a dose of 716.7 mg crude drug/kg. This dose was considered appropriate because oral administration of EYFZ into human is traditionally 43 g crude drug/60 kg/day.

Evaluation of survival, tumor size, and body weight of tumor-bearing mice Colon-26 (5×10^5) cells were subcutaneously implanted into 6-week-old mouse at once, and simultaneously the oral administration of EYFZ was started. Control mice received the same volume of saline instead of EYFZ. Thereafter, the survival of these mice was monitored everyday for evaluating the life-prolonging effect. The tumor size and body weight were examined 2-3 times a week. The major axis (a) and minor axis (b) of the tumor were measured, size was estimated by using the formula $ab^2/2$[17].

Assay of splenic NK cell activity The splenic NK cell activity of tumor-bearing mice was determined by lactate dehydrogenase (LDH) assay[18,19]. The spleen cell suspension was prepared by squeezing the spleen between two glass slides. The distilled water was added to the spleen cell suspension for provoking lysis of red blood cells. After washing three times with serum-free basal medium, the cells were incubated in a 25 cm^2 culture flask (FALCON, Becton Dickinson) in serum-free basal medium at 37 ℃ in a 5 % CO_2 incubator for 2hr to remove adherent cells. The non-adherent cells were collected as effector cells. Effector cells (5×10^6 cells/ml) were incubated with NK-sensitive target cells, YAC-1 (5×10^4 cells/ml), in a total volume of 0.2 ml/well using 96 well round bottomed microplate (IWAKI Glass Co, Ltd.). An effector-target ratio of 100:1 was considered optimum. The plate was incubated for 4 hr at 37 ℃ in a 5 % CO_2 incubator. After incubation, 0.05 ml of the supernatant from each well was collected, then used for LDH assay to determine the cytotoxic activity using the LDH cytotoxic Kit (Wako Pure Chemical Industries, Ltd.). The percentage of specific release was calculated according to the following formula: % specific lytic activity = (experiment release - spontaneous release) / (maximum release - spontaneous release) × 100.

Table 1. The Botanical Origins of Crude Drugs of "Ekki-Youketsu-Fusei-Zai"

Crude drug	Botanical origin (Family name)	Harvesting time	Representative defined compounds	Ratio
Astragali Radix	* *Astragalus membranaceus* Bge. Var. *Ongholicus* (Bge.) *mongholicus* (Bge.) Hsiao (A. *mongholicus* Bge.) * *Astragalus membranaceus* (Fisch.) Bge.	spring or autumn	β-sitosterol, D-β-Asparagine, disaccharide, 2'-4'-dihydroxy-5,6-dimethoxy-isoflavane, calycosin, formononetin, astragaloside Ⅰ.Ⅱ.Ⅲ.Ⅳ	10.0 g
Zizyphi Fructus	**Ziziphus jujubc* (Rhamnaceae)	autumn	Sugar, phlegm, malic acid, tartaric acid	5.0g
Amomi Semen	* *Amomum villosum* Lour. * *Amomum Xanthioides* Wall.	autumn	Borneol, dextrogyric camphor, bornyl acetate, linalool, nerolide	5.0g
Angelicae Radix	* *Angelic sinensis* (Oliv.) Diels	autumn	Ligustilide, n-butylidene-phthalide, sesquiterpenes A.B, carvacrol	8.0g
Cervi Parvum Cornu	* *Cervus nippon* Temminck * *Cervus elaphus* L.	spring or autumn	Ceramide, oestrone, 17-β-Estradiol	5.0g
Rehmanniae Radix	* *Rehmannia glutinosa* Libosch.	autumn	Catalpol, stachyose, amino acid, β-Sitosterol	10.0g

Medicine was prepared by blending the crude drugs in the ratios indicated above.

Statistical analysis Survival curve was determined using the method of Kaplan and Meier, and the log rank test was used to calculate the significance. Other data were statistically analyzed based on the Student's t test, and the differences were recognized significant with p value less than 0.05. The results were expressed as mean ± standard deviation (SD).

Results

We first examined the effect of oral administration of EYFZ on the survival of tumor-bearing mice. When EYFZ (716.7 mg crude drug/kg/day) was continuously administrated to the mice which had been implanted subcutaneously with colon-26 for 28 days, the life-prolonging effect was found as shown in Fig. 1. All of tumor-bearing mice in the control group that received only the saline died within 59 days after the onset of this experiment (Fig. 1). On the other hand, the tumor-bearing mice treated with EYFZ showed a significant life-prolonging effect as compared to the control ($p < 0.01$), and died in 70 days on average.

Secondly, we compared the tumor size of EYFZ-administered group mice with that of control group mice. The tumor size, as described in Materials and Methods, was calculated by measuring the major (a) and minor (b) axis of formed tumor tissue based on the formula $ab^2/2$. Result obtained from observation for 34 days revealed that the tumor size in EYFZ-administrated mice was smaller than that in the control mice (Fig. 2). Although the tumor size on day-13 was almost similar to that in the control, those on day-20 and on day-27 were clearly smaller than that in the control group ($p < 0.5$ and $p < 0.1$, respectively).

Thirdly, we examined the effect of oral administration of EYFZ on the body weight in tumor-bearing mice. When we observed the body weight of mice in the EYFZ-treated or control mice successively for 28 days after the onset of this experiment, it was shown that the body weight in the EYFZ-treated mice was much larger than that in the control mice (Fig. 3). Particularly, the body weight in the treated mice was significantly larger than that in the control mice on day-14 ($p < 0.05$).

Finally, we examined the effect of oral administration of EYFZ on splenic NK cell cytotoxicity in tumor-bearing mice. We found that the NK cytotoxic activity of splenic cells in orally EYFZ-administrated mice was significantly higher than that in control mice on the day-17 and day-24 after the onset of transplantation and oral administration, as shown in Fig. 4 ($p < 0.01$).

Discussion

In this experiment, we examined whether EYFZ, one of the TCMs, affected the anti-tumor activity in mice into which the murine colon-26 carcinoma cell line was subcutaneously implanted. This colon-26 cell line, an undifferentiated carcinoma induced by the carcinogen N-nitroso-N-methylurethan, has been successfully used as the model of tumor-bearing mice and cachexia[17, 20]. In our study, colon-26 cells could grow well after subcutaneous implantation into the normal BALB/c mice. Oral administration of EYFZ caused a statistically significant prolonging effect on survival in tumor-bearing mice as compared with the control mice. We also examined both the tumor size and body weight. The tumor size in EYFZ-administrated mice was shown to be much more decreased than that in the control mice. Particularly, the tumor size in the treated mice after 27 days became significantly smaller than that in the control. Hence, it is suggested that the oral administration of EYFZ was more effective compared with oral administration of saline for both the survival and the decrease of a tumor size in tumor-bearing mice.

The cachexia, an exhaustive state with severe weight loss, is a serious problem in cancer patients affecting their morbidity and mortality. It lowers their quality of life and shortens their life-span[21, 22]. Colon-26 cell line has been successfully used as the model of such cachexia by tumor growth[17]. Thus, we observed the body weight of tumor-bearing mice everyday following the subcutaneous implantation of colon-26 cells into both the EYFZ-treated and the control mice. Results clearly showed that oral administration of EYFZ led to the better increase of body weight as compared to the control without EYFZ. Though the body weight of the control mice was lower than that of the EYFZ-treated mice, initially, it finally reached the similar level to that of the EYFZ-treated mice. This means the tumor growth in the control mice leads to the increase of body weight. We think the difference of the body weight between two groups of mice on day-14 is much more important that on the later days, and it reflects improvement of cachexia by EYFZ. However, since there was a possibility that EYFZ influenced the increase of the body weight of cancer-bearing mice from the nutritious viewpoints, it will be necesarry to further examine the effect of oral-administration of EYFZ on the body weight of the normal mice without cancer cell in the future.

NK cells exhibit spontaneous cytotoxic activity in a non-major histocompatibilty complex (MHC) restricted manner against virus-infected cells and cancer cells *in vivo* and their activity can be augmented by administration of interferon-γ (IFN-γ)[21-24]. Some papers

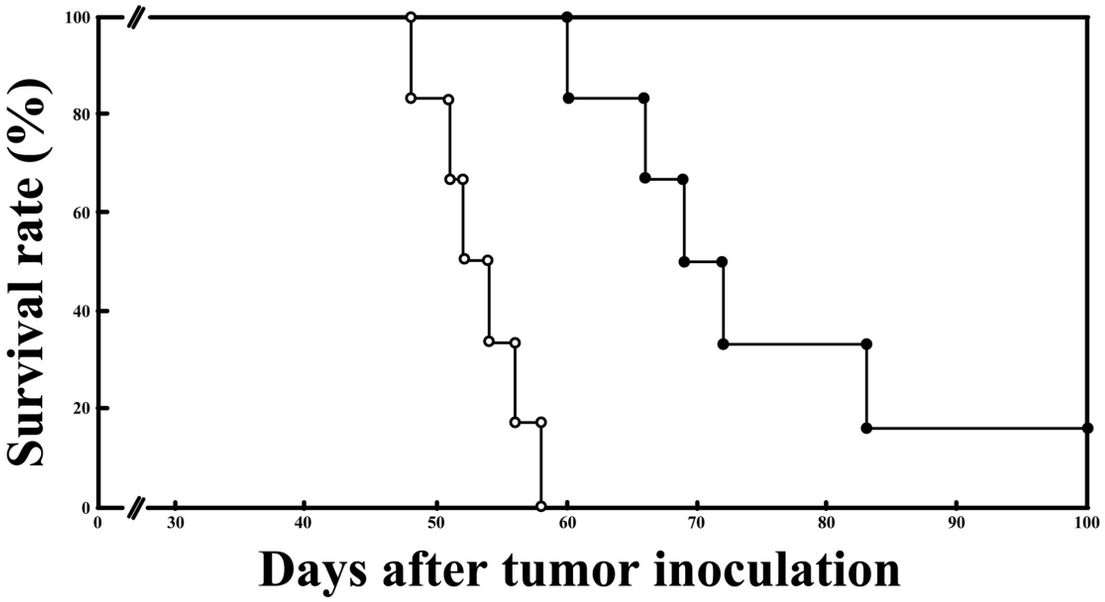

Fig. 1. Effect of Ekki-Youketsu-Fusei-Zai (EYFZ) on survival of mice inoculated with colon-26 cells. Six BALB/c female mice per group were inoculated s.c with colon-26 (5×10^5 cells/mouse). Treatment group mice were orally administered with EYFZ (716.7 mg crude drug/kg) for 28 days just after the subcutaneous implantation of colon-26 cell line. The control group mice received only saline. Their survival rates are shown. ( ): treatment group mice, (○): control group mice. $P<0.01$; by log rank test.

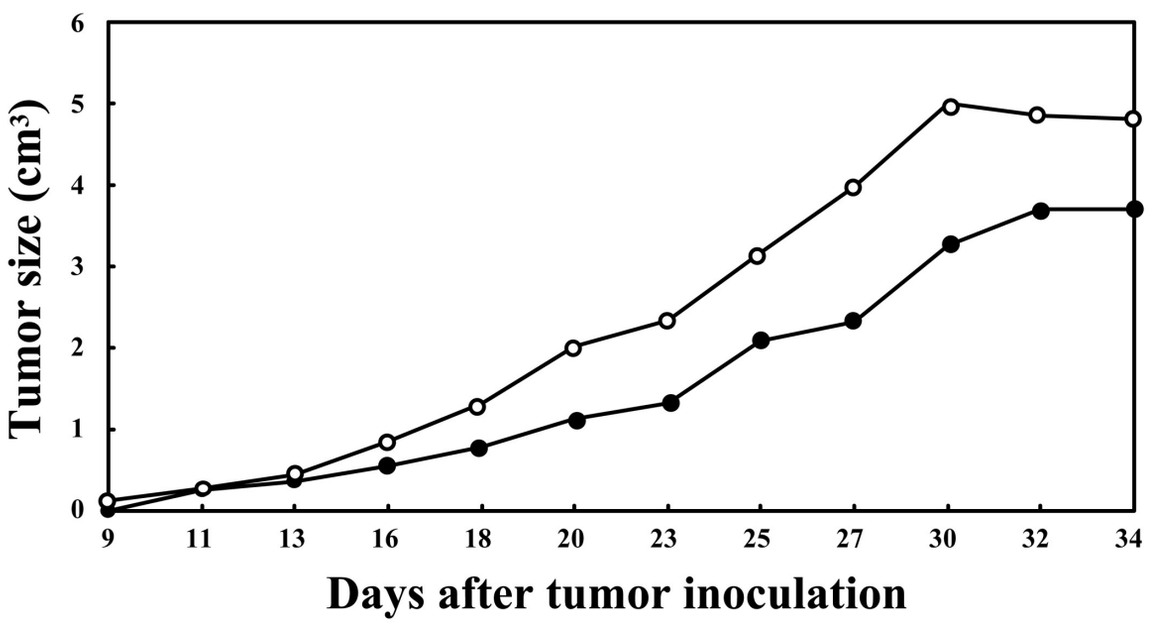

Fig. 2. Effect of Ekki-Youketsu-Fusei-Zai (EYFZ) on the *in vivo* growth of colon-26 tumor cells. Mice treated with EYFZ (716.7 mg crude drug/kg) and control mice without EYFZ were inoculated with colon-26 cells according to the same protocol as in Fig. 1. Tumor growth was measured after implantation and calculated as shown in Material and Methods. The tumor size was measured from day-9 to day-34 after transplantation. ( ): treatment group mice, (○): control group mice.

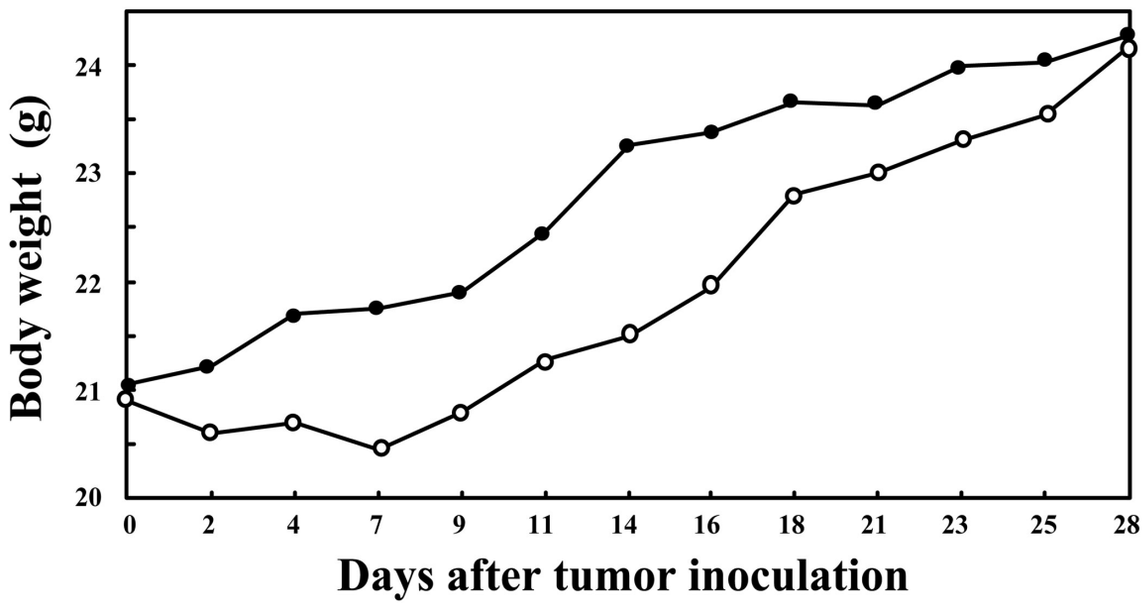

Fig. 3. Effect of Ekki-Youketsu-Fusei-Zai (EYFZ) on body weight loss of mice inoculated with colon-26 cells. Mice treated with EYFZ (716.7 mg crude drug/kg) and control mice without EYFZ were inoculated with colon-26 cells according to the same protocol as in Fig. 1. After implantation, the body weight was measured 2 or 3 times a week and finally on day-28. ( ): treatment group mice, (○): control group mice.

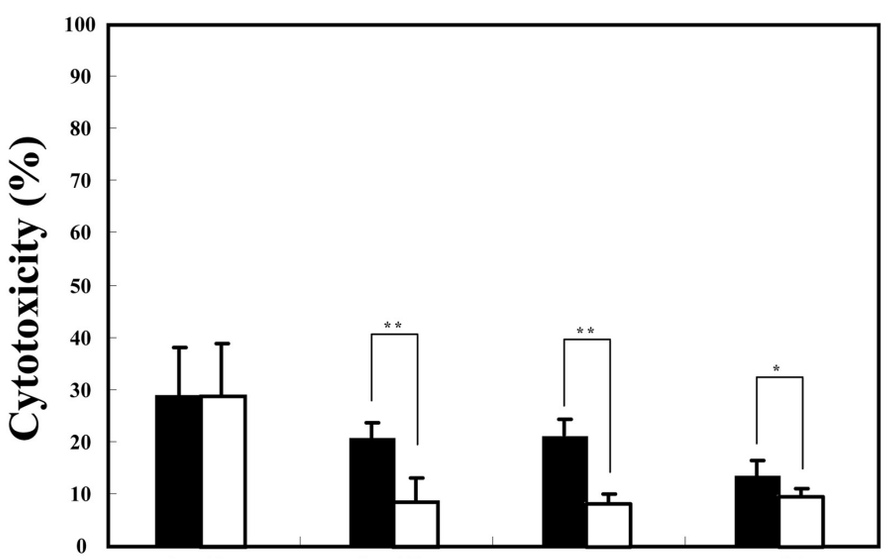

Fig. 4. Effect of Ekki-Youketsu-Fusei-Zai (EYFZ) on NK cell activity of mice inoculated with colon-26 cells. Five BALB/c female mice per group were inoculated s.c with colon-26 cells (5×10^5 cells/mouse). Treatment group mice were orally administered with EYFZ (716.7 mg crude drug/kg) for 28 days just after the subcutaneous implantation of colon-26 cell line. Control group mice received only saline. Each column and vertical bar represents the mean±standard deviation of 5 mice on day-10, day-17, day-24 and day-31 after inoculation. ( ): treatment group mice, (□): control group mice. *P<0.5 and **P<0.01; by Student's two-tailed test.

showed that some kinds of crude drugs and TCMs exert anti-tumor effects by activation of NK cells[13, 25-29]. Therefore, we also tried to examine the cytotoxic effect of oral administration of EYFZ on splenic NK cell activity in tumor-bearing mice on day-10, day-17, day-24 and day-31 following the subcutaneous implantation of colon-26 cells. Results clearly showed that the NK activity of spleen cells in orally EYFZ-administrated mice was significantly higher than that in control mice on the day-17 and day-24 after transplantation and oral EYFZ administration. Those results suggest the possibility that EYFZ has the anti-tumor effect on colon-26 implanted mice via augmentation of NK cell activity. In our present experiment, it was hard to investigate the cytokine production of NK cells in the spleen due to the insufficient number of splenic NK cells. However, as the NK activity was clearly augmented in the EYFZ-treated mice, further evaluation for EYFZ in anti-tumor activity seems to be needed by examining the effect of oral-administration of EYFZ on the cytokine production of NK cells in the spleen.

EYFZ does not show the direct cytotoxicity on some tumor cell lines including colon-26, A549 and Kato III (data not shown). This greatly suggests that the efficacy of EYFZ on survival and tumor-growth in tumor-bearing mice is attributable to the enhancement of host defense or immune system such as NK cell activity but not to the direct cytotoxicity against tumor cells. The efficacy of biological response modifier (BRM) in cancer therapy has been attributed to its activating functions on immune system including neutrophils, macrophages, NK cells, and cytotoxic T cells as well as on various cytokines. Therefore, it would be important to investigate further the effect of EYFZ on the immune system. This point is currently being pursued in detail in our laboratory.

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中国の伝統的漢方薬「益気養血扶正剤」の抗腫瘍活性と免疫細胞機能に及ぼす影響
1. 担癌マウスにおける延命効果とNK細胞機能の促進

Deng Hong[1, 2)]，中島かおり[1)]，Ma Xinling[1)]，蓮見賢一郎[1)]，赤塚俊隆[2)]，和合治久[3)]

中国の伝統的漢方薬である「益気養血扶正剤」（オウギ，ジュクジオウ，トウキ，ジュクシャ，タイソウ，ロクジョウの6種類から構成される：以下EYFZと略す）の抗腫瘍活性と免疫細胞機能に及ぼす影響を知る目的で，第1にcolon-26腫瘍細胞株を移植した担癌マウス（BALB/c）を用いて，28日間のEYFZ経口投与が担癌マウスの延命とNK細胞機能にいかなる影響を与えるかについて追究した．実験の結果，EYFZを連続的に投与された担癌マウスの寿命は非投与群と比較して有意に延命することがわかった．特にEYFZの経口投与によって，腫瘍サイズと体重の減少が抑制された．一方，担癌マウスの脾臓細胞を採取して，その中のNK活性を知るためYAC-1細胞への細胞傷害活性をLDH（lactate dehydrogenase）アッセイによって調べた結果，EYFZを投与された担癌マウスでは，非投与群と比較して有意にNK活性が高まることが判明した．これらの結果から，EYFZにはcolon-26を移植された担癌マウスの延命を引き起こす抗腫瘍効果があり，その作用機構の一つにNK活性の亢進のあることが示唆された．

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〔平成13年4月24日 受付〕